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Molecules as Mechanical Machines. Genetic Algorithms in the Search of Appropriate Descriptions of Molecular Catalysts

Gottfried Huttner, Johan Friedrich, Axel Frick, Volker Schulz, Jörg Karas, Johannes Hunger, and Stefan Beyreuther

Anorganisch Chemisches Institut
Universität Heidelberg, 69120 Heidelberg, Germany
E-mail: g.huttner@indi.aci.uni–heidelberg.de

The development of selective organometallic molecular catalysts is one of the most promising areas of molecular chemistry and which presently developes at an unforeseen and still increasing pace. Organometallic molecular catalysts have a unprecedented selectivity which is only paralleled by the astounding selectivity of biological catalysts the enzymes. Organometallic catalysts make use of the same type of so called secondary interactions as enzymes to reach this selectivity. They make use of well designed surfaces which embed the catalytic centre and orient the reagent by secondary interactions. The orientation between the catalytically active centre and the substrate is pre–organised in such way that only one of many possible products will result. For the rational design of an organometallic catalyst the knowledge of the secondary interactions is a pre–requisite therefore. Since this type of interaction can not be reliably calculated by quantum mechanical methods for large molecules chemists have to use other types of models, the most promising approach being the force field model which describes a molecule in terms of a mechanical machine. The potentials which are necessary to describe the stiffness of the different types of springs and joints of such a model have to be inferred from experimental data. Force fields describing organic molecules have been developed and are highly successful in modelling and predicting the behaviour of organic compounds. On the other hand force field models for the description of organometallic compounds which would be based on as many experimental data as available are not generally known. The paper describes the development of an appropriate force field for a class of rhodium compounds which are activein enantioselective catalysis by a novel approach. The parameters of all potentials involving contributions by the rhodium atom are optimised by Genetic Algorithms on the basis of as many experimentally determined structures as available. The efficiency of of this approach is demonstrated by the comparison of calculated and experimental data with respect to different shapes of the catalyst to their transformations into each other. Predicted and observed energies are found to agree within a few kJ/mol. These results recommend the approach chosen as a tool for the rational design of organometallic catalysts.

1 Introduction

Life is based on the interaction of molecules. The regulation of the intricate processes of life is based on the capability of molecules to recognise each other. How can a molecule, which has no intellectual capability, recognise at all? In the molecular regime, recognition is based on the interaction between molecular surfaces. Imagine a ball rolling over a plane and imagine, that the plane has some sticky area. The ball will roll and roll until it comes to that sticky place where it will be stuck. In the language of molecular recognition this would be interpreted as if the ball had recognised the sticky area, or, vice versa, as if the sticky area had recognised the ball. The two have recognised each other.

Molecules have very many different kinds of highly selective sticking areas. As everybody knows from daily life, there are different types of glues for different combinations

of materials. Some types of glues will be highly adhesive for plastic materials while others will stick to metals and again others will be good for bricks. The propensity of all these types of glues to stick especially well to certain types of materials is based on the interaction of the gluing material with the surface of the materials, which have to be stuck together.

Likewise with molecules: The surfaces of molecules are structured such that they will be attractive to certain types of molecular surfaces, indifferent to some other kinds and even repulsive to yet other types. Attraction, indifference and repulsion result from so called secondary interactions. Such interactions are far weaker than chemical bonds. This means, they are easily made and broken again at normal temperatures and only if a few of them are made at a time, the total of such contacts will be strong enough to survive thermal motion. Thermal motion is a condition met in nature. The game of molecular recognition is solved in nature by making a highly developed use of these weak secondary forces.

Our life relies upon those well–optimised chemical interactions in biological systems. Modern daily life relies as well to a large extent on the availability of man made chemical products. Such products are made by transforming natural products such as crude oil, silica or lime stone, to name just a few, into products which, in most cases have no resemblance to the sources which they have been made from. This kind of "transsubstantiation", which appears almost mystical at the first glance, is brought about by whole series of well–designed chemical reactions. The individual chemical processes used in industry are tuned such as to give the highest possible selectivity. Selectivity means that in a well designed chemical process the input chemicals will transform selectively into just the one desired output chemical. In the ideal solution to the problem of selectivity, there would be no waste products, whatsoever, and the output chemical could be used without the need of any further sort of purification as such.

Such an ideal process describes the maximum obtainable economic profit as the minimum environmental costs. The processes, which are used in producing bulk chemicals, even though being painstakingly optimised, are generally far from this goal.

The chemical processes in living nature, on the other hand, are generally very close to this goal. They tend to work with 100% selectivity, with a minimum of energy consumption and a minimum of waste products. The chemical systems working in living systems have been optimised by the evolutionary process over billions of years. The tricks played by these natural systems achieve extreme selectivity and efficiency and rely upon the highly developed use of secondary interactions. The molecules of life are structured such that they are able to recognise each other. Chemicals are transported to specific places in a living organism by virtue of them being recognised as just the very kind of molecule which is needed at a specific place. At this specific place, which is often an enzyme, i.e. a biological catalyst, the molecules are transformed with 100% selectivity into products, which the body has need of. No waste, no unnecessary expenditure of energy. Chemistry of life has solved the selectivity problem to an extent which man made chemistry is in many cases still far off. However, chemists know how to approach the degree of perfection by which the chemistry in living systems is characterised. They know that they have to make use of secondary interactions between molecules, to cope with the problem.

Chemists have found that organometallic catalysts present an elegant solution to many of the major selectivity problems. In such organometallic catalysts a metal centre is embedded in a cavity made up from innocent and unreactive constituents which are able to

form a well structured but, nevertheless, flexible cover on one side of the metal. The metal is the reactive centre in these catalysts. It sits there and waits for a substrate molecule to approach it and as soon as the substrate molecule is close enough, the metal will start to "digest" it. Digesting means it will either cut it into pieces at specific positions and release the fragments or it will stick together two molecules and then release the product. By this way the metal is free to start a new catalytic cycle grabbing and digesting as soon as the products of this process are released.

Such a catalyst may work like a kind of sewing machine making long chain molecules from small substrate molecules in sewing one piece to the other again and again. High tech polymers are made by just this approach routinely, nowadays. In other types of metal mediated reactions which are brought about by the organometallic catalysts new functionalities are added to the substrate molecules at specific places in a highly specific orientation. The specificity of such organometallic catalysts relies upon the specificity of the secondary interactions between the scaffolding which builds up the periphery of the metal — chemists call this "the ligands" — and the substrate molecule. Only substrate molecules which fit well into the cavity formed by the scaffolding will have the chance to approach the metal close enough such as to undergo the reaction with it.

One may imagine the channel leading from the outside of the organometallic catalyst to the metal in its interior as a highly structured surface with sticky points there and there and repulsive points at other places. This highly structured channel will orient the substrate molecule such that there is only one way for it to approach the metal. This is the reason for the extremely high selectivity which may be achieved by organometallic catalysis. The development of such catalysts, the improvement and the development of rules which allow for a rational design of specific catalysts are topics which are at the centre of state of the art molecular chemistry. This statement is underlined by the fact that the 2001–Nobel Price in chemistry has been given to three chemists, all of them being intimately involved in the design and optimisation of organometallic catalysts.

The problem with designing specific catalysts has still, by and large, to be solved by trial and error methods. While it is often known how a specific metal activates a substrate molecule and how it brings about the appropriate transformation it is not so well known how the secondary interactions in the periphery of the metal will influence the kind of approach of the substrate molecule to the metal. The individual steps of the transformation occurring at the metal may, nowadays, be quite reliably modelled by quantum mechanical calculations. Secondary forces, however, are not easily computed by quantum mechanical approximations even by the most modern techniques. Chemists have to rely on other types of models if they wish to rationalise the effect of secondary interactions within these models. One of these approaches is based upon the idea that a molecule with all its different building blocks and linkages between them might be described as a kind of mechanical machine with balls and joints and gears quite like a mechanical machine in the visible world[1]. In order to describe the response of such a mechanical machine on a stimulus it is necessary to have a precise plan of its architecture and a precise knowledge of the stiffness of the joints and of all the springs acting within it.

Transferring this idea to the description of the behaviour of the molecules is straightforward in so far as the architecture of molecules is well known to a very high degree of accuracy from structure analyses. Bonds between atoms have to be replaced by springs of a certain stiffness, or, to put it into other words, a bond between two atoms is simu-

lated by a potential curve centred at the average distance of this kind of bond, where the potential function is described by only a few parameters. In many cases the harmonic potential, characterised by just one single force constant, will do. The angles, subtended by two bonds which radiate from one and the same atom, the so called valence angles, may be treated by the same approach as may the torsion around the central bonds of a four atom arrangement, the so called torsion angle. The forces between two atoms which are not bonded to each other, may be modelled by Lenard–Jones–type potentials made up of attractive and repulsive potential terms.

The problem in describing molecules as Pico molecular machines results from the fact that the force constants describing the stiffness of all the flexible parts of a molecule are not known from the beginning. Nevertheless, sets of potential functions with the appropriate force constants have been developed which produce a consistent description of the properties of organic molecules within the force field approach. This type of "molecular mechanics" model has been developed into a reliable tool for the prediction of properties of organic molecules and is now routinely used in every day organic chemistry[1].

Modelling of organometallic compounds, on the other hand, is impeded by the fact that no reliable potentials are available for describing the interaction between a metal and its immediate neighbourhood, its ligands. Organometallic compounds which are active in catalysis will generally make bonds to carbon atoms, hydrogen atoms, nitrogen atoms and so on, but none of the relevant potentials is known a priori.

There is yet another problem in the application of molecular mechanics methods to organometallic molecules: Different from the constituents of organic molecules (carbon atoms, hydrogen atoms, nitrogen and oxygen atoms) for which only a very limited set of co–ordination types (linear, triangular, tetrahedral) is found in nature, metals show many different types of co–ordination. It is far more difficult, therefore, to standardise these potentials, since every individual type of atom in a specific type of surrounding will have to be described by a specific set of potential functions[3].

One way around this problem is to restrict the model to a specific class of compounds all of which having the same co–ordination number and type and to try to develop appropriate force field parameters for this specific type of compound. If the type of compound chosen is a reactive one and if sufficient experimental data are available for the structures and reactivities of this set of compounds one may try to develop a force field description of this set of molecules and then try to correlate the results of molecular mechanics calculations with observed properties. This approach has been taken in the project which is described here in very short terms.

2 The Chemical Problem

If an object in three–dimensional space consists of a minimum of four different sub–objects and if these sub–objects may be ranked according to one or the other of their properties, this object defines a sense of rotation in $\mathbb{R}^3$.

For this phenomenon the term chirality is used amongst chemists. Molecules are three–dimensional objects and they contain chemically different groups in different positions. If, as it is often the case, their symmetry is low, they define a definitive sense of rotation as soon as different groups are ranked.

This means, that such chiral molecules exist as pairs with the only difference between

the members of a pair lying in their right–handedness or left–handedness or, as chemists say, in their chirality. Many of the molecules which are active in biological systems are chiral molecules. Pharmaceuticals, which have to interact with the molecules of life, will cause different biological responses depending on their chirality. There are many examples of drugs where it is known that only one type of chirality causes a beneficial response while the other one, the enantiomeric form – as chemists say- may either have no detectable response at all or, even worse, a detrimental response. Lack of appreciation of this fact may cause severe problems, one such example being thalidomide where one enantiomere is extremely helpful while the other one is extremely teratogenic. The lack of knowledge of this fact has caused a lot of suffering. Another example where one enantiomere is biologically active while the other one is inactive, is the so called L–dopa but which is one of the major curatives in Parkinson's disease. Only one enantiomere, as chemists say, the L–form, L–dopa, is active, while the other enantiomere, D–dopa, is inactive. It is clear, therefore, that for production of pharmaceutical compounds it is essential to make use of selective synthetic processes which selectively produce only the desired enantiomeric form of a compound.

The solution to this kind of problem came about only in the last decades. Organometallic catalysts of pre–designed chirality are the key to this solution. The work discussed in this paper has its roots in just this field. During the preparative synthetic work of the group it had been found that certain chiral ligands are easily prepared in just the desired enantiomeric form and that these ligands may engage in bonding to a rhodium centre. As it was known that rhodium compounds are active catalysts in the production of compounds like L–dopa the catalytic properties of such rhodium compounds have been analysed. When the novel chiral rhodium compounds were used as catalysts, the following observation was made: Starting from achiral unsaturated substrates, saturation — i.e. addition of two hydrogen atoms to the unsaturated substrate — occurs with a selectivity of up to 91% with respect to the formation of just one enantiomere of the product[4].

The metal–ligand part consists of the rhodium centre and the chiral ligand and the co–ligand part consists of an eight–membered hydro–carbon cycle — during catalysis the metal–ligand part persists while the place occupied by the co–ligand (Fig. 1) will hold the reaction species. Within the metal ligand part the rhodium atom, the two phosphorus atoms and the three carbon atoms of the chain make up a six–membered cycle. This cycle is chiral since at the central carbon atom symmetry is broken by the presence of one OH–substituent and one H–substituent at this atom (Fig. 1). The two phosphorus atoms contain two further substituents each. These substituents are again different, one substituent group consisting of so called mesityl residues (i. e. phenyl residues substituted by three methyl groups Me) in a symmetrical way , the other substituent group consisting of phenyl entities (Fig. 1).

Within the part containing the co–ligand consists of an eight–membered carbon hydrogen cycle which is bonded to the rhodium centre by the interaction between the rhodium atom and its double bonds (Fig. 1). This eight–membered cycle is just kind of a protective group. During the catalytic process itself this cycle is replaced by substrate molecules and hydrogen. The catalytic species which does the real work is thus different from the stable and fully characterised compound and this is the reason for the convention followed by chemists to call such a compound a pre–catalyst as it is a molecule from which the active catalyst will be formed during the catalytic process itself.

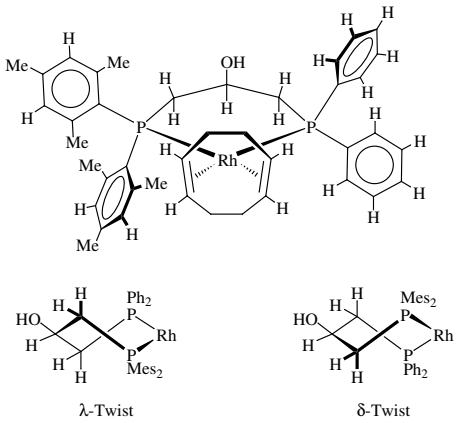

Figure 1. Chemical formula of the catalytically active chiral rhodium compound. The three–dimensional architecture and the transition between geometrically different forms of this compound were predicted by force field methods in quantitative agreement with experimental data. The "pre–catalyst" molecule consists of two parts — a metal ligand part containing the rhodium centre, the two phophorus atoms and all the groups linked to them. This ligand part stays intact during the catalytic cycle. The other part of the compound contains an eight–membered hydro–carbon cycle as a protective group which is replaced by the reactants during catalysis. The six–membered cycle formed by the ligand and the metal is capable of existing in different forms. The forms shown (λ–twist, δ–twist, bottom) are both chiral and are the low–energy "conformations" of this cycle.

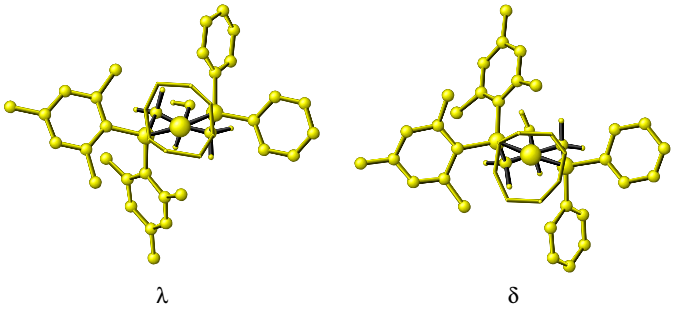

Figure 2. Projection of the two low–energy structures of the catalytic compound which differ in the conformation of the metal–ligand cycle (λ–twist form, δ–twist form).

The interesting part of the molecule is the six–membered cycle (Fig. 1, bottom). This six–membered cycle exists in two enantiomeric forms, as structure analyses and NMR–analyses clearly demonstrate[4,10]. The two forms differ in the type of twist of their scaffolding and are chiral, therefore. Were it not for the chiral substitution of the central carbon atom (HO, H, CH_2PMes_2, CH_2PPh_2) the two forms — which chemists call λ– and δ–forms — would of course be of equal energy. The given sense of chirality at the central carbon atom which has been pre–determined by the synthesis of the ligand will create an energy difference between these two forms. Imagine a pair of hands of two partners. Both right hands fit nicely together as do both left hands. But there is a kind of misfit between the left hand of one partner and the right hand of the other one or vice versa. The fit and

the forces acting between these two chiral objects is different for these two types of pairs. The energy difference between the two different twist forms of the six–membered cycle — caused by the chirality around the central carbon atom of the chain — is still small enough to be overcome by the thermal energy at ambient temperatures ($\Delta E \approx 4$ kJ/mol) and is also small enough to allow for the co–crystallisation of both forms in one and the same crystal (Fig. 2).

Even if the energy difference between the enantiomeric species is as low as 4 kJ/mol the selectivity in imprinting the chirality of the catalyst molecule to the substrate upon reaction with it is up to 91%. Any understanding of how this high selectivity comes about must be based on an understanding of the flexibility of the six–membered cycle and the motions of the phosphorus substituents connected with it. To this end a detailed experimental NMR–Study was performed by which the structure of the compound in solution and the inter–conversion of the λ– and δ–forms of the chelate cycle with all it's geometrical and energetical implications has been extracted in a quantitative way[10]. These experimental results form a sound basis for evaluating the results of any computational approach. In order to solve, at least, part of the chemical problem, namely to rationalise the structures and the flexibility of the pre–catalyst, a force field model for this set of compounds was developed[6].

3 The Computational Problem

A force field model tries to describe a molecule in the sense of a mechanical machine. While the force field — i.e. the potentials to describe the properties correctly — for the organic part of the pre–catalyst is well known and sophistically evaluated, that part of the force field which describes the interaction of the metal with the ligands, is unknown from the beginning.

The necessary condition for any sensible force field description of this part is that this description has to reproduce the observed structures of compounds of the class to which the pre–catalyst belongs. Even if this condition is not necessarily sufficient for the prediction of energetic differences between different geometric forms of one an the same molecule a good agreement may be found that it might well be so. An approach was chosen therefore, which consists in optimising the force constants of all those potential functions to which the metal is an immediate contributor. To make this approach work it is necessary to determine as many structures within a given family of compounds such as to have enough variance in the relevant data and a broad enough data base to make such a refinement process appropriate.

In a series of papers[5] referring to the statistical basis of this approach as well as to the application of this approach to organometallic molecules, it has been shown that the results obtained this way are well in accord with the observations, both with respect to the prediction of the shape of molecules and to the prediction of energy differences between different forms of molecules.

The basic mathematical problem opposing this kind of approach is the lack of any optimisation method which could lead to an optimal solution with certainty within a finite number of steps. While "global optimisation" cannot be brought about by any mathematical method in its true sense with certainty, optimisation by Genetic Algorithms is a highly efficient approach with this kind of optimisation problem. In fact the approximation of

Genetic Algorithms[2] as well as the merits of Neural Network Analysis in this field had first been demonstrated in the series of papers cited[5]. The optimisation problem consists in finding the optimal values of all the force constants which imply a contribution by the metal for as many compounds of a given class as possible at a time.

The evaluation criterion has to be based on some measure of the distance between the computed structure and the observed structure in n–dimensional space. By using Genetic Algorithms as the optimisation tool this evaluation has to be done for any compound in the data set for any parameter set within a population over all generations over and over again.

This is a heavy load even for nowadays computing machines and is only feasible in a parallel computing environment. The great advantage of the Genetic Algorithm in this respect is that it is naturally parallel. This means that the evaluation of fitness, which is the really time consuming part of the procedure since it calls for a full force field optimisation in each step — may be performed at different processors at a time. Collecting the evaluation results and setting up a next generation for the Genetic Algorithm needs practically no time.

In order to perform the necessary computations, a force field program written in "C" by Tan[7] was appropriately modified and embedded in different shells which allow its use in parallel computing environments[5,6]. The Genetic Algorithm program package was taken from "PGAPack"[8]. Parallelisation was achieved by making use of the "MPI" library[9].

By using this type of approach, force field parameters for the description of all those interactions involving the rhodium atom in compounds of the type of the pre–catalyst were optimised on the basis of 11 crystallographically determined structures of compounds of this class. Based on these parameters a complete search in the conformational space of the pre–catalyst was performed.

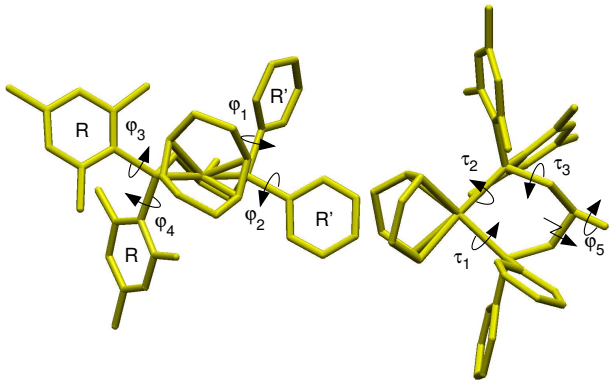

Figure 3. Definition of the conformational space of the catalytically active compound. After optimising the force field model on the basis of 11 compounds of this general type a full grid search in the eight–dimensional conformational space was defined by $\phi_1 - \phi_5$ and $\tau_1 - \tau_3$ performed.

The conformational space was defined by the rotational positions of the aryl groups ($\phi_1 - \phi_4$, Fig. 3), a set of torsion angles within the six–membered cycle ($\tau_1 - \tau_3$, Fig. 3) and the rotational position of the OH–group (ϕ_5, Fig. 3). A complete search within this eight–dimensional conformational space is again time consuming and is greatly speeded

up by the use of parallel computers. Sorting the 10000s of results such that a kind of adiabatic hyper–surface may be constructed is an organisational problem which has been solved by writing the appropriate code.

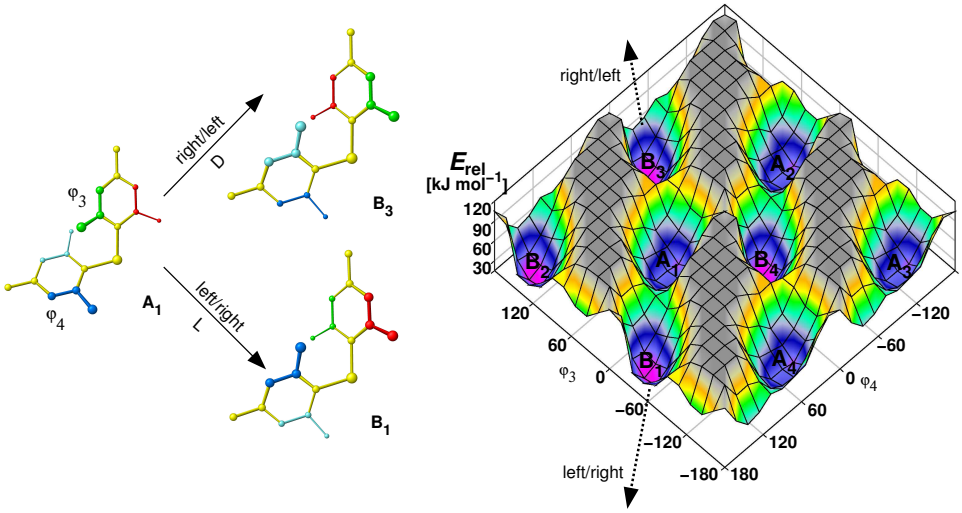

Figure 4. Interconversion of λ– and δ–forms of the catalytically active compound is accompanied by a strictly coupled rotation of the aryl groups at ϕ_3/ϕ_4. The projection of the hyper–surface onto the ϕ_3/ϕ_4 co–ordinate plane reveals that two energetically slightly different low–energy pathways exist. This coupled prediction of a rotation is in full agreement with the experimental findings.

The result of this analysis in shown in figures 4 and 5. Figure 4 shows a projection of the relevant hyper–surface on to the ϕ_3/ϕ_4 co–ordinate plane. ϕ_3 and ϕ_4 refer to the rotation of the mesityl substituents. It is seen (Fig. 4) that the two mesityl groups rotate in a strictly coupled manner such that if ϕ_3 rotates in a clockwise sense, the rotation of ϕ_4 is counter–clockwise. The two rotational pathways: ϕ_3 clockwise ϕ_4 counter–clockwise, (right/left in Fig. 4 label D) and the opposite sense rotation: ϕ_3 counter–clockwise, ϕ_4 clockwise (left/right in Fig. 4, label L) are of slightly different energy (Fig. 4). This finding is in complete agreement with the NMR observations[10].

By the complete analysis of the eight–dimensional conformational space of the pre–catalyst it was found that the δ–form of the cycle is 3.1 kJ/mol more stable than the λ–form (Fig. 5) in almost numerical agreement with the experimental value of 3.4 kJ/mol for this energy difference. The least energy pathway of this type of transformation was as well analysed by force field methods and by experimental NMR techniques. An activation energy of around 69 kJ/mol was calculated — again in excellent agreement with the experimental value of 64.4 kJ/mol (Fig. 5).

4 Conclusion

Highly reliable and predictive force field models describing the behaviour of organometallic compounds may be developed on the basis of the relevant structural data of as many

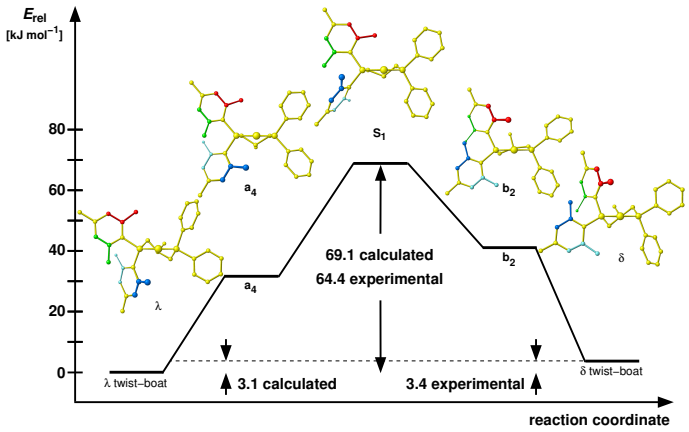

Figure 5. Characteristic steps during the transition of the λ–form of the catalytically active compound into its δ–form. The energy difference between these two forms is calculated as 3.1 kJ/mol with the λ–form being the most stable one. The experimental value for this difference is 3.4 kJ/mol. The calculated activation barrier is 69.1 kJ/mol. Again this value is in excellent agreement with the experimental value of 64.4 kJ/mol.

compounds of a given family as possible.

The force constants describing the interactions with the metal as derived by their optimisation using genetic algorithms together with the known force field parameters of the organic parts of such molecules are able, when fed in to the appropriate force field program, to reproduce the static as well as the conformational behaviour of such molecules in excellent agreement between experimental and calculated data.

With respect to the documented high reliability such specific force fields are an efficient tool for the detailed analysis of catalytic processes mediated by organometallic catalysts.

5 Acknowledgment

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